DIACOMIT® (stiripentol) Drug Interactions

Documented and potential drug interactions with DIACOMIT

Cytochrome P450 Enzyme & Transporter-Mediated Drug Interactions[1-10]	Clinical Relevance
CYP1A2 substrates (eg, theophylline, caffeine)	DIACOMIT is both an inhibitor and an inducer of CYP1A2. Plasma concentrations of CYP1A2 substrates may increase or decrease.
CYP2B6 substrates (eg, sertraline, bupropion, cyclophosphamide, ketamine, methadone, tamoxifen, selegiline, thiotepa)	DIACOMIT is both an inhibitor and an inducer of CYP2B6. Plasma concentrations of CYP2B6 substrates may increase or decrease.
CYP3A4 substrates (eg, midazolam, triazolam, quinidine, oral contraceptives, HIV protease inhibitors, antihistamines, calcium channel blockers, statins, codeine, clobazam)	DIACOMIT is both an inhibitor and an inducer of CYP3A4. Plasma concentrations of CYP3A4 substrates may increase or decrease.
CYP2C8 substrates (eg, loperamide, pioglitazone)	Increased plasma concentrations of CYP2C8 substrates (DIACOMIT inhibits enzyme activity)
CYP2C9 substrates (eg, NSAIDs, phenytoin, sulfonylureas, warfarin, sildenafil)	Increased plasma concentrations of CYP2C9 substrates (DIACOMIT inhibits enzyme activity)
CYP2C19 substrates (eg, diazepam, clopidogrel, citalopram, omeprazole, norclobazam)	Increased plasma concentrations of CYP2C19 substrates (DIACOMIT inhibits enzyme activity)
P-glycoprotein (P-gp) substrates (eg, carbamazepine)	Increased plasma concentrations of P-gp substrates (DIACOMIT inhibits transporter activity)
Breast Cancer Resistance Protein (BCRP) substrates (eg, methotrexate, prazosin, glyburide)	Increased plasma concentrations of BCRP substrates (DIACOMIT inhibits transporter activity)
Strong CYP1A2, CYP3A4, or CYP2C19 inducers (eg, rifampin, primidone, phenytoin, phenobarbital, carbamazepine)	Decreased plasma concentrations of DIACOMIT (DIACOMIT is metabolized by CYP1A2, CYP2C19, CYP3A4)
CYP2D6 substrates (eg, amitriptyline, citalopram, paroxetine, clozapine, haloperidol, risperidone, thioridazine, beta-blockers, opioid analgesics, dextromethorphan)	No clinically relevant interactions observed.

INDICATION

DIACOMIT (stiripentol) capsules for oral use or powder for oral suspension are indicated for the treatment of seizures associated with Dravet syndrome in patients 2 years of age and older taking clobazam.

There are no clinical data to support the use of DIACOMIT as monotherapy in Dravet syndrome.

To report suspected adverse reactions, contact BIOCODEX at 1-866-330-3050 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

This card is not intended to provide medical advice and is not a replacement for experienced clinical judgment.

Please see full DIACOMIT Prescribing Information inside pocket.

DIACOMIT®
(stiripentol) 250 mg, 500 mg
capsules or powder for oral suspension

DIACOMIT® (stiripentol) Drug Interactions

Concomitant antiepileptic drugs

Antiepileptic Drug	Interaction
Clobazam	In two double-blind, placebo-controlled trials, there was a 2- to 3-fold increase in clobazam and a 5-fold increase in norclobazam plasma concentrations when DIACOMIT was added to clobazam. When DIACOMIT was initiated, the dose of clobazam was 0.5 mg/kg/day administered as a divided dose twice daily. In the event of clinical signs of side effects (ie, drowsiness, hyperexcitability) the clobazam daily dose was reduced by 25% each week.[11]
Valproate	The potential for metabolic interaction between DIACOMIT and valproate is considered modest; no modification of valproate dosage is needed when DIACOMIT is added, except for clinical safety reasons. In two double-blind, placebo-controlled studies, the daily dose of valproate could be decreased by 10 mg/kg daily in case of loss of appetite.[11,12]
Topiramate	In a long-term study, a significant percentage of patients were receiving topiramate in combination with DIACOMIT. Based on the clinical observations in this group, there is no evidence to suggest that a change in topiramate dose and dosage schedule is needed when topiramate is co-administered with DIACOMIT.[11]
Levetiracetam	Levetiracetam does not undergo hepatic metabolism to a major extent. No pharmacokinetic drug interaction between DIACOMIT and levetiracetam is anticipated. However, the combination may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating.[11,13]
Carbamazepine*	In clinical trials in which DIACOMIT was added to carbamazepine, increases of carbamazepine concentrations were observed. Adverse events, including dizziness, ataxia, and diplopia, typically subsided when the carbamazepine dose was decreased. A dose reduction is recommended.[11,12,14]
Phenytoin*	Using DIACOMIT together with phenytoin may alter the blood levels of both medications. DIACOMIT levels may decrease. At the same time, DIACOMIT may cause the blood levels of phenytoin to increase. Dose adjustment may be needed.[13]
Phenobarbital	Using DIACOMIT together with phenobarbital may alter the blood levels of both medications. DIACOMIT levels may decrease. At the same time, DIACOMIT may cause the blood levels of phenobarbital to increase. Dose adjustment may be needed.[13]
Cannabidiol	Adding DIACOMIT to a regimen containing cannabidiol (CBD) results in no change in CBD levels and clinically insignificant increases in 7-OH-CBD.[15]
Primidone	Using DIACOMIT together with primidone may alter the blood levels of both medications. DIACOMIT levels may decrease. At the same time, DIACOMIT may cause the blood levels of primidone to increase. Dose adjustment may be needed.[13]
Rufinamide	Rufinamide may reduce the blood levels of DIACOMIT, which may make the medication less effective. Dose adjustment of DIACOMIT may be needed.[13]
Zonisamide	Zonisamide is metabolized via CYP3A4; coadministration with DIACOMIT, which inhibits CYP3A4, may result in increased plasma concentrations of zonisamide. Dose adjustment may be needed.[1,5,13]
Oxcarbazepine*	Oxcarbazepine may reduce the blood levels of DIACOMIT, which may make the medication less effective. Dose adjustment may be needed.[13]
Lamotrigine*, Felbamate, Gabapentin, Pregabalin, Perampanel, Ezogabine (Retigabine), Eslicarbazepine, Brivaracetam, Vigabatrin*	Using any of these antiepileptic drugs together with DIACOMIT may increase side effects such as dizziness, drowsiness, confusion, and difficulty concentrating.[13]
Fosphenytoin	Fosphenytoin used in combination with DIACOMIT may alter the blood levels of both medications. The blood levels of DIACOMIT may decrease, while DIACOMIT may cause the blood levels of fosphenytoin to increase. Dose adjustment of both medications may be needed.[13]
Ethosuximide	DIACOMIT may increase the blood levels and effects of ethosuximide. Dose adjustment may be needed.[13]
Tiagabine	DIACOMIT may increase the blood levels and effects of tiagabine. Dose adjustment may be needed.[13]

*NOTE: These medications often exacerbate seizures in patients with Dravet syndrome and should be avoided.[16]

References: 1. DIACOMIT® [prescribing information]. Beauvais, France: BIOCODEX, Inc.; August 2018. **2.** Hedrich WD, Hassan HE, Wang H. Insights into CYP2B6-mediated drug-drug interactions. *Acta Pharm Sin B*. 2016;6(5):413-425. doi:10.1016/j.apsb.2016.07.016. **3.** DIACOMIT® [summary of product characteristics]. Gentilly, France: BIOCODEX, Inc.; January 2014. **4.** Backman JT, Filppula AM, Niemi M, Neuvonen PJ. Role of cytochrome P450 2C8 in drug metabolism and interactions. *Pharmacol Rev*. 2016;68(1):168-241. doi:10.1124/pr.115.011411. **5.** Patsalos PN, Perucca E. Clinically important drug interactions in epilepsy: general features and interactions between antiepileptic drugs. *Lancet Neurol*. 2003;2(6):347-356. doi:10.1016/s1474-4422(03)00409-5. **6.** Chamsi-Pasha H. Sildenafil (Viagra) and the heart. *J Family Community Med*. 2001;8(2):63-66. **7.** Triplitt C. Drug interactions of medications commonly used in diabetes. *Diabetes Spectrum*. 2006;19(4):202-211. doi:10.2337/diaspect.19.4.202. **8.** Tran A, Rey E, Pons G, et al. Influence of stiripentol on cytochrome P-450-mediated metabolic pathways in humans: in vitro and in vivo comparison and calculation of in vivo inhibition constants. *Clin Pharmacol Ther*. 1997;62(5):490-504. doi:10.1016/s0009-9236(97)90044-8. **9.** DIACOMIT® American Product Monograph. BIOCODEX, Inc.; September 2019. **10.** Data on file, BIOCODEX, Inc.; 2019. **11.** DIACOMIT® Canadian Product Monograph. Biocodex SA; December 2012. **12.** Chiron C, Marchand MC, Tran A, et al. Stiripentol in severe myoclonic epilepsy in infancy: a randomised placebo-controlled syndrome-dedicated trial. *Lancet*. 2000;356(9242):1638-1642. doi:10.1016/s0140-6736(00)03157-3. **13.** Stiripentol Drug Interactions. Drugs.com. https://www.drugs.com/drug-interactions/stiripentol.html. Accessed April 22, 2020. **14.** Perez J, Chiron C, Musial C, et al. Stiripentol: efficacy and tolerability in children with epilepsy. *Epilepsia*. 1999;40(11):1618-1626. doi:10.1111/j.1528-1157.1999.tb02048.x. **15.** Morrison G, Crockett J, Blakey G, Sommerville K. A phase 1, open-label, pharmacokinetic trial to investigate possible drug-drug interactions between clobazam, stiripentol, or valproate and cannabidiol in healthy subjects. *Clin Pharmacol Drug Dev*. 2019;8(8):1009-1031. doi:10.1002/cpdd.665. **16.** Wirrell EC, Laux L, Donner E, et al. Optimizing the diagnosis and management of Dravet syndrome: recommendations from a North American consensus panel. *Pediatr Neurol*. 2017;68:18-34.e3. doi:10.1016/j.pediatrneurol.2017.01.025.

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